BJA
British Journal of Anaesthesia

Anaesthesia, Surgery and Life-Threatening Allergic Reactions: Protocol and methods of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists

Journal:	*British Journal of Anaesthesia*
Manuscript ID	Draft
Article Type:	Special article
Date Submitted by the Author:	n/a
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Mesh keywords:	Anaphylaxis, Perioperative, Methods

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Running head: NAP6: Protocol and methods

Wordcount

Abstract 250

Paper 4461

Abstract

Background: Anaphylaxis during anaesthesia is important for patients and anaesthetists.

Method: The 6th National Audit Project of the Royal College of Anaesthetists examined the incidence, predisposing factors, management and impact of life-threatening perioperative anaphylaxis. NAP6 included: a national survey of anaesthetists' experiences and perceptions; a national survey of allergy clinics; a registry collecting detailed reports of all Grade 3-5 perioperative anaphylaxis cases for one year; and a national survey of anaesthetic workload and perioperative allergen exposure. National Health Service (NHS) and independent sector (IS) hospitals were approached to participate. Cases were reviewed by a multi-disciplinary expert panel (anaesthetists, intensivists, allergists, immunologists, patient representatives and stakeholders) using a structured process designed to minimise bias. Clinical management and investigation were compared with published guidelines. This paper describes detailed study methods and reports on project engagement by NHS and IS hospitals. The methodology includes a new classification of perioperative anaphylaxis and a new structured method for classifying suspected anaphylactic events and the degree of certainty with which a causal trigger agent can be attributed.

Results: NHS engagement was complete (100% of hospitals). Independent sector engagement was limited (13% of approached hospitals). We received >500 reports of Grade 3-5 perioperative anaphylaxis, with 266 suitable for analysis. We identified 199 definite or probable culprit agents. Antibiotics (47%) were the most common cause of perioperative anaphylaxis, followed by neuromuscular blocking agents (33%); chlorhexidine (9%) and patent blue dye (4.5%). Latex anaphylaxis was not reported.

Conclusions: The methods of NAP6 are robust and support the accompanying papers.

Keywords: anaphylaxis; anaesthesia; allergy; National Audit Project

Life-threatening allergy during anaesthesia and surgery (perioperative anaphylaxis) is a subject of importance to both patients and clinicians.[1] Importance relates to the impact on patient safety and in relation to specific subsets of patients or drugs.[1]

A number of factors mean that data from historical studies or from other geographical locations may not be transferrable to current practice or UK practice. No major prospective study of perioperative anaphylaxis has been performed in the UK.

The National Audit Projects of the Royal College of Anaesthetists have an established role in examining clinically important, rare complications of anaesthesia that are incompletely studied.[2-7] The established methodology of the NAPs is to perform a national survey or surveys of relevant national activity[8,9] and establish a national registry for reporting of relevant cases for a time-limited period. This enables an examination of (a) pre-existing practices and beliefs (b) relevant activity (denominator data) and (c) a large cohort of relevant cases (numerator data) and thence (d) incidence data.

Methods

The 6th National Audit Project (NAP6) was commissioned by the Health Services Research Centre (HSRC) of the National Institute of Academic Anaesthesia for the Royal College of Anaesthetists (RCoA). It is the sixth in a series of 'national audits' (though more correctly described as service evaluations) conducted by the specialty.[10].

The topic for NAP6 was selected by open tender for proposals in 2013. There were 91 proposals covering 33 topics.[11] The topic of perioperative anaphylaxis was selected by a committee comprised of members of the HSRC executive board.

The intention of the project was to establish

- What proportion of cases of suspected perioperative anaphylaxis is referred and or investigated?
- What proportion of investigated cases is proven or unproven?
- How well does management, referral and investigation match published guidelines?
- Is there any correlation between drugs used in resuscitation, e.g., adrenaline, alpha agonists vasopressin and outcome for severe cases?

The methodology of NAP6 is similar to, and builds upon, that used for NAP3-5.[2,3,5]

The NAP6 project was approved by Confidentiality Advisory Committee of the NHS Health Research Authority (HRA), National and Local Caldicott Scrutiny Process in Scotland and Privacy Advisory Committee for Northern Ireland. The Confidential Advisory Committee deals with approvals for the handling of patient-identifiable information across the NHS. If such information is required, then approvals are required under Section 251 of its governance procedures. Since no patient-identifiable information was used, no section 251 application was necessary. The National Research Ethics Service (NRES) confirmed it to be a service evaluation, not requiring formal ethical approval. The project received the endorsement of all four Chief Medical Officers of the UK.

All hospitals in the UK performing surgical procedures with anaesthetist involvement were contacted. This included 356 UK National Health Service hospital centres and 304 Independent Sector hospitals believed to perform surgical work. All NHS centres volunteered a Local Co-ordinator (LC), a consultant anaesthetist who became responsible for delivering the project at their hospital and for liaising with the central NAP6 team. Several LCs were responsible for more than one hospital within a Trust (England, Northern Ireland) or Board (Scotland, Wales). During efforts to engage with the Independent Sector Hospitals more than 300 hospitals were contacted on several occasions.

There were four elements to the project. First, a baseline survey collected retrospective data on anaesthetists' previous experiences with perioperative anaphylaxis and their perceptions and patterns of risk-avoidance.[9] Second, UK allergy clinic services were surveyed to identify clinics that investigated suspected perioperative anaphylaxis and to compare their practices against guidelines.[12] Third, the main prospective study collected anonymised case reports over a one-year period. Fourth, a prospective survey, also in 2015, collected comprehensive information on workload, demographics and patients' exposure to potentially-allergenic drugs and other substances during anaesthesia and surgery.[13]

LCs were sent detailed information (available at http://www.nationalauditprojects.org.uk/NAP6-Resources#pt) and were tasked with disseminating and co-ordinating all phases of the project locally.

All allergy clinics investigating perioperative anaphylaxis were contacted and informed of the project. Materials were made available to enable them to give LCs detailed information about tests performed and their results when investigating suspected perioperative anaphylaxis.

LCs were asked to ensure the reporting of all cases of suspected life-threatening perioperative anaphylaxis to the NAP6 team. Anaphylaxis was defined as a severe, life-threatening, generalized or systemic hypersensitivity reaction. Perioperative anaphylaxis was defined as

> *Anaphylaxis which occurs in patients undergoing a procedure requiring general or regional anaesthesia or sedation or managed anaesthesia care (anaesthetist monitoring only) under the care of an anaesthetist between the period of first administration of a drug (including pre-medication) and the post-procedure transfer to the ward, or critical care.*

As we only wished to collect cases of life-threatening anaphylaxis it was emphasised that only anaphylaxis grades 3-5 (table 1) were to be included. Cases were to be included irrespective of age or hospital location, but patients in critical care or the emergency department were excluded unless undergoing procedural general anaesthesia.

(Table 1 near here)

Each month the LC was required to provide the central NAP6 team with a 'return' indicating the number of reports of suspected life-threatening perioperative anaphylaxis identified that month, using a system developed by the UK obstetric surveillance system[14] and also used in NAP5.[5] Where no reports were received the LCs returned a 'nil' report.

Presentations, posters and promotional material were provided to each LC and the project was widely advertised nationally (Figure 1). Information provided to LCs included advice on interpretation of grades of anaphylaxis and a series of 'frequently asked questions', with answers. For example, LCs were advised to regard hypotension that was mild or required modest doses of a vasopressor or fluid as meeting the definition of Grade 2, whereas hypotension that was profound, sustained, resistant to treatment or requiring extensive treatment met the criteria for grade 3.

(Figure 1 near here)

Reporting cases

Reporting was in two parts.

Part A included details of the patient, drugs administered, the clinical features, management and timings relating to the event, outcomes, contributory factors, referral for investigation and details of reporting of the event and communication to the patient. LCs were to asked submit part A as soon as possible after the suspected anaphylactic event. Definitions of clinical features associated with anaphylaxis required to be reported were provided in the webpage supporting information (Supplementary Table 1).

Part B was to be completed by the LC, after allergy clinic investigation was complete. It included full details of allergy clinic investigations, sought to confirm patient outcomes, and to update the data on reporting to national registries and information given to patients. Part B was not required fro fatalities.

Between them, the two parts of the case reporting form collected detailed information on all aspects of the event and patient care. The questions are not reproduced here but are available at http://www.nationalauditprojects.org.uk/NAP6-Data-Entry#pt

Cases were included if the event occurred between 00.00 hrs on 5th November 2015 and 23.59.59 hrs on 4th November 2016. Reports were accepted until May 2017 to allow for allergy clinic waiting times.

Case reporting was confidential. When an LC or other anaesthetist wished to report a case, they contacted the NAP6 administrator. The reporter was required to confirm

- This was a case of suspected perioperative grade 3-5 anaphylaxis, as defined above.
- The case occurred in the data collection period.
- Whether the case took place in an NHS or independent sector hospital.

After confirmation that the case met inclusion criteria, the reporter was issued with a unique identifier and password. These were used to submit case details to a password protected, secure and encrypted website. Before accessing the webform the LC was required to change their password. Cases arising from NHS and independent sector hospitals were assigned different numbers for easy identification. No patient, clinician or hospital data was admissible, and the webpages repeatedly reminded reporters not to include such information

The NAP6 administrator could track progress of reporting (not started: started but incomplete; complete; submitted) but could not access forms. Once completed and submitted the anonymised form was automatically transferred electronically to the project clinical lead, who was able to raise

queries and receive replies about case reports via a blind email (i.e. he was blinded to where the email went to or from where replies came). No other panel members received reports or had access to the website. In this manner, no panel member was aware of the geographical origin of any case, nor of any individuals involved in managing the case.

A moderator, a consultant anaesthetist with appropriate expertise, was available to discuss cases when there was uncertainty about inclusion. The moderator was not on the review panel and had no contact with the review panel throughout the project.

Review of cases

The NAP6 panel met monthly to review and classify cases. The panel was comprised of representatives of patient support groups, patient representatives, and clinicians in relevant fields (anaesthesia, critical care, allergy, immunology) representing stakeholder and subspecialty organisations. Clinicians were selected by stakeholder organisations and while many had specific expertise in allergy, this was not a requirement for joining the panel.

The panel reviewed each case in detail and in a structured manner, three times. First, the clinical care (Part A) was reviewed by a small group of 3-5 clinical and patient representative panel members. Second, allergists and immunologists reviewed drug administration and allergy investigations (relevant parts of Part A and all of Part B). Several groups performed these tasks on different cases concurrently. The outputs of the reviews were used to populate a structured output form (Appendix 1) and spreadsheet for subsequent analysis. When sufficient cases were reviewed, all groups joined into a large panel, of typically 12-15 panel members, and the cases were again reviewed to combine the outputs of the clinical and allergy/immunology reviews and to check and moderate each small group's findings.

This process was used in an attempt to avoid 'outcome bias' (where the known poor outcome leads to an unreasonably harsh judgement),[15] 'hindsight bias' (where retrospective review leads to a tendency to believe that an adverse outcome was predictable or avoidable)[16] and 'groupthink' (where a desire to agree within groups leads to a lack of independent scrutiny).[17]

In judging quality of care, we referred to guidelines from: the Association of Anaesthetists of Great Britain and Ireland on management of suspected anaphylaxis associated with anaesthesia;[18] the Resuscitation Council (UK) on management of anaphylaxis;[19] the European Resuscitation Council on cardiopulmonary resuscitation;[20] and the British Society for Allergy and Clinical Immunology (BSACI) guidelines on investigation of anaphylaxis during general anaesthesia.[21] In addition, the review panel

referred, where appropriate to *NICE CG183 Drug allergy: diagnosis and management of drug allergy in adults, children and young people*.[22,23] and *NICE CG134 Anaphylaxis: assessment and referral after emergency treatment*[24]

As these guidelines were used to measure deviation from standards of care, NAP6 had a greater genuine 'audit' component than previous NAPs. Overall quality of care (initial management, clinic referral by anaesthetist and allergy clinic investigation) were also each judged as 'good', 'poor', 'good and poor' or 'unassessable' based on adherence to guidelines and ultimately by panel consensus.

It became rapidly apparent that cardiopulmonary resuscitation (CPR) was frequently not started when there was profound hypotension. We therefore defined a systolic blood pressure, below which we judged that CPR should be started, which we set at 50mmHg (see discussion). These cases were classified as grade 4. When CPR was not started, we judged this as failure to initiate CPR when indicated and judged this to be a deviation from resuscitation guidelines.

The case report form included specific questions about potential errors related to allergy history or administration of cross reacting substances. Preventability of each case was classified as 'yes', 'no', 'uncertain' and reasons why the event may have been prevented were recorded.

Patient outcomes were measured in two ways. Individual patient outcomes were captured on the case report form including new anxiety about future anaesthetics, features consistent with post-traumatic stress disorder, change in mood, impaired memory, impaired coordination, impaired mobility, myocardial infarction, heart failure, renal impairment and stroke. Overall severity of patient outcome, was recorded using the National Patient Safety Agency classification of severity of harm from patient incidents (Table 2).[25] In most cases Grade 3 anaphylaxis itself meets the definition of moderate harm. When resuscitation had only involved minimal doses of vasopressor or other drugs and no further action taken the case was deemed to meet the criteria for minimal harm. Apparently permanent sequelae (i.e. persisting symptoms or deficits at follow-up) were recorded as severe harm, as were cardiac arrest and ICU stay >14 days.

(Table 2 near here)

Each event was classified as 'allergic anaphylaxis', 'non-allergic anaphylaxis', 'anaphylaxis mechanism uncertain', 'anaphylaxis uncertain' or 'not anaphylaxis' using the classification shown in Table 3. For each classification certainty of classification was recorded as high or intermediate.

(Table 3 near here)

In order to classify the type of each event, a definition of mediator release was required. Providing mast cell tryptase samples were taken at appropriate times after the event (broadly: soon after the event and approximately 1-3 hours after the event and a baseline sample either taken before the event or ≥24 hours after the event) the following definition was used:

- Peak mast cell tryptase ≥1.2x nadir value + 2μg.L^{-1} [26] or
- Peak mast cell tryptase ≥14 μg.L^{-1} (i.e. >99th centile for normal mast cell tryptase levels)[27]

This was a pragmatic definition and made in the knowledge that the second part of the definition might not fully exclude a very small number of cases of mastocytosis.

Where there was uncertainty, differential diagnoses other than anaphylaxis were carefully considered by both clinicians and allergist/immunologists.

In determining adequacy of allergy clinic investigation, BSACI guidelines[21, 28,29] were used by the immunologists and allergists to set the following rules.

- Where testing for allergy to neuromuscular blocking agent (NMBA) was necessary, given variable access to some NMBA the NAP6 minimum panel[12] was applied: suxamethonium, rocuronium and either atracurium or cis-atracurium should have been tested and at least one safe alternative should have been sought.
- Chlorhexidine and latex should have been investigated routinely because of the widespread risk of exposure.
- For SPTs and intradermal tests (IDTs) to be judged appropriate, there should be no tests performed that were not indicated. This was to exclude 'scatter-gun' testing being judged as good practice.
- Allergy to antibiotics and particularly beta-lactams could only be excluded if a negative skin test was followed by negative provocation testing

The allergists and immunologists reviewed each case that was confirmed to be anaphylaxis, to determine all possible causative agents (culprits). Reviewing the clinical data and allergy clinical tests, they identified these drugs as having high, intermediate or low culpability.
We recorded 'identified culprits' as follows

- Definite: where one sole agent was recorded with a high degree of confidence and any other agents with intermediate or low confidence.
- Probable: (a) where only one agent was recorded with an intermediate degree of confidence and any other agent was identified with low confidence (b) where two agents were both recorded with a high degree of confidence.
- Possible: where two agents were recorded with an intermediate degree of confidence and none with a high degree of confidence.
- Do not count: (a) where more than two agents were recorded with a high degree of confidence (b) where more than two agents were recorded with an intermediate degree of confidence (c) where the only agents recorded were identified with a low degree of confidence.

Agents meeting the criteria for definite or probable were considered to be 'identified culprits': agents meeting the criteria for possible or do not count, were not.

Approximately 10-12 cases were fully reviewed each day in the early part of the review process, increasing to up to 22 in the latter stages as the panel became more familiar with the process. Due to the high number of cases submitted we were not able to perform full reviews of all cases. The remaining cases in the main dataset had a limited review that determined: the diagnosis of anaphylaxis, the grade of anaphylaxis, all potential culprits and 'identified culprits'.

Results

The results of the Allergy clinic survey,[9] Anaesthesia Baseline survey,[12] Anaesthetic Activity survey[30] and Allergen survey[13] are each reported separately and are not considered further here. There were no technical or security breaches of the website, or concerns about identification of patients, clinicians or hospitals.

All 356 (100%) NHS hospitals where surgery was undertaken agreed to take part in the project and volunteered an LC. These 356 hospitals were served by 282 LCs. Eighty four percent of NHS hospitals returned all monthly reports: overall return rate of 'monthly reports' from NHS hospitals was 94%.

Responses were considerably fewer from independent sector hospitals. In total 41 (13%) independent sector hospitals volunteered to participate and these hospitals were included in data collection. Thirty nine percent of these independent sector hospitals returned all monthly reports: overall return rate of 'monthly reports' from these independent sector hospitals was 70%.

In view of the small number of independent sector hospitals that agreed to participate it was decided that this sample would not be representative of practices or events in this healthcare sector and a decision was made to include their data only for examination of isolated events and not for numerical analysis.

The full results of analysis and findings of reports of anaphylaxis are presented in the accompanying papers.[31,32] We present here the results of the NAP6 process.

There were 628 requests made for login details to the reporting website. A total of 541 cases were submitted: 412 with part A and part B completed, 125 with only part A completed and four with only part B completed. Amongst these there were seven requests for an identifier for the reporting website from independent sector hospitals but only two cases were fully reported. These cases were not included in the main dataset.

Only those cases with part A and part B (n=256), or deaths (n=10) were considered for review. Of these 93 were not suitable for review due to lack of detail or not meeting entry criteria; 27 were uninterpretable; 15 were not anaphylaxis; nine were excluded as being grade 2 anaphylaxis: two were from independent sector hospitals.

A total of 266 NHS cases met inclusion criteria, were interpretable and were grade 3-5 anaphylaxis: these formed the main dataset.

A total of 217 cases were fully reviewed, including 184 of the main dataset. The remaining 82 cases underwent limited review, as described above.

Amongst the 266 cases in the main dataset, there was an identified culprit in 192 cases. In seven cases there were two identified culprits (all because two agents were identified with high confidence) so the total number of identified culprits was 199 (Table 4).

(Table 4 near here)

Discussion

NAP6 is likely to be the most comprehensive prospective study of perioperative anaphylaxis ever undertaken. It provides prospective data on a large number of cases which have all been subject to structured multidisciplinary expert review. It provides the opportunity to learn about preparedness of hospitals and clinicians, clinical presentation of perioperative anaphylaxis, severity, immediate management, referral for investigation, and outcomes. It provides significant epidemiological data about distribution of anaphylaxis grade, suspected and actual triggers, and non-standard treatments. Further, it provides data on the quality of management and investigation in a 'real world setting' and of communication, between clinicians and to patients.

In order to collect and analyse this data in a meaningful manner it was important to perform a structured analysis of cases. That structure was underpinned by clear definitions of which events should be included or excluded and also by classification during review. We followed the review process previously used in other NAPs which included multiple, serial, multidisciplinary reviews incorporating patient representation, formal moderation and a structured output. Review of events that have already happened is always prone to the limitations of 'looking backwards' and this may be exacerbated when the outcome of the event is known.[15-17] Our processes made every effort to produce balanced judgements, accepting these known limitations.

Anaphylaxis is 'a severe, life-threatening generalised hypersensitivity reaction.'[33] Lesser hypersensitivity reactions should not be included in the term anaphylaxis. Unlike many previous large-scale studies of hypersensitivity we have focussed only on genuinely life-threatening reactions (i.e. true anaphylaxis). We judged this would enable us to gather the most clinically powerful lessons, to improve engagement in the project and to increase capture rates. These are also the cases where most is to be gained (or lost) in efforts to improve care.

There are numerous gradings scales and definitions of severity of hypersensitivity/anaphylaxis and the cut-offs between grades vary considerably. This has implications for data analysis and comparisons between studies. Ring and Messmer's 1977 classification included four grades with grade 3 'shock, life-threatening spasm of smooth muscles (bronchi, uterus etc)' grade 4 'cardiac and/or respiratory arrest'.[34] Garvey in 2001 described only three grades with the highest grade (grade 3) including all 'Very severe reactions requiring prolonged treatment, e.g. anaphylactic shock, usually, but not always, involving two or more organ systems'.[35] Mertes in 2003 included in grade 3 life threatening events 'cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm' and in grade 4 'circulatory inefficacy, cardiac and/or respiratory'.[36] In 2007 Kroigaard introduced grade 5: fatal anaphylaxis.[37] Consensus diagnostic criteria for definition of anaphylaxis

was reported in 2006 but have significant limitations if applied to perioperative anaphylaxis.[38] In 2010 yet another classification was published - classifying all hypotension as grade 4.[39]

Despite this apparent surfeit of grading systems, we found none entirely clear or satisfactory and developed the classification shown in table 1. This classification aimed specifically to accommodate the normal variations in vital signs and physiology that can be seen in the perioperative setting, particularly in elderly, frail or co-morbid patients. The NAP6 classification of perioperative (hypersensitivity and) anaphylaxis uses the pragmatic terms 'unexpected' and 'severe' in the belief that anaesthetists can distinguish the usual from the unusual, and a reaction requiring rescue treatment from one which does not. We used a clear cut off for grade 4 i.e. if indications for initiating CPR are fulfilled. During the NAP6 project another group published a new classification and this also usefully reviews many of the existing classifications and their limitations in respect to perioperative anaphylaxis.[40] This used three grades A-C: grade A is non life-threatening and therefore does not meet the accepted definition of anaphylaxis and grade B includes some grade 2-3 characteristics of other groups, grade C being similar to Kroigaard's grade 4.

During early case reviews it became apparent that 'indication for CPR' might not be as clear-cut as we had thought. The case report form asked both for the lowest blood pressure recorded and whether CPR was started. In a large number of cases the lowest blood pressure was very low, often being <60mmHg or <50mmHg or even unrecordable, but CPR was not performed. This was discussed at length in the panel. We took external expert advice, from experts in resuscitation, anaphylaxis and their guidelines and concluded that, it was logical to set a lowest systolic blood pressure at which it was reasonable that CPR should start, in adult patients. In the awake patient it is now routine to start CPR when 'there are no signs of life/signs of responsiveness'. As perioperative anaphylaxis most commonly takes place after induction of anaesthesia, these signs are absent. In invasively monitored patients a blood pressure of <50mmHg is predictive of central and peripheral pulselessness[41] which should trigger CPR. As non-invasive blood pressure monitors tend to over-estimate the blood pressure in severe hypotension, a non-invasive blood pressure recording of <50mmHg implies the true blood pressure is even lower. We therefore judged that when the lowest systolic blood pressure was <50mmHg, CPR was indicated. This rule was then applied to all cases. These cases were recorded as grade 4, and if CPR was not started recorded as 'CPR not started when indicated'. We also judged this a deviation from (resuscitation) guidelines and recorded whether this was the only such deviation. This group of patients (lowest systolic blood pressure and no CPR) were examined as a separate cohort to explore whether their outcomes differed from other patient groups.[27] The

NAP6 classification of grade of anaphylaxis was therefore updated to include this critical blood pressure cut-off (Supplementary table 2).

In the analysis of investigation of anaphylaxis the allergists and immunologists on the panel required a clear way to classify the type of immunological event and devised that shown in Table 3. The presence of a dynamic tryptase rise was determined using an accepted consensus method,[26] which has (since NAP6 started) been confirmed to have high specificity (78%), positive predictive value (98%) and a moderate negative predictive value (44%) in perioperative anaphylaxis.[42] Where there was no dynamic rise in tryptase we used a value of >99th centile as indicating elevation: this has been shown to improve sensitivity of the above test.[27] This goes well beyond previous reports which have often simply classified cases as '*IgE mediated* – hypersensitivity with skin prick test positive; *non IgE-mediated* – hypersensitivity with skin prick test negative, or *unclassified*'. Assessing utility and quality of allergy clinic investigation was further aided by including the consensus view that the NAP6 panel of NMBAs[12] should be used and that allergy to both chlorhexidine and latex allergy should be tested routinely because of their widespread (and often hidden) presence in healthcare settings.[12,21, 43,44] Finally we used a structured method to define the degree of certainty with which culprit agents were identified and only included those that were definite or probable culprits in reporting our findings.

The published guidelines selected for providing standards against which the quality of practice was assessed[18-22] were chosen to encompass immediate resuscitation (including of cardiac arrest), secondary clinical management, referral to an allergy clinic, primary and specialist allergy investigation, record keeping, and communication with patients and healthcare professionals. United Kingdom guidelines were selected, being the most relevant to the patient population being studied.

Using this method, we received >500 reports of perioperative anaphylaxis. We were able to analyse 266 cases and identify 199 culprit agents in 192 cases. Our findings include the important observations that: antibiotics (47%) are a more common cause of perioperative anaphylaxis than neuromuscular blocking drugs (33%); chlorhexidine (9%) and patent blue dye (4.5%) were prominent triggers; latex was not (0%). These findings are discussed in context and full numerical analysis in the accompanying paper[28] and in the full report.

As with previous NAPs, NAP6 is the product of a concerted national effort by all departments of anaesthesia in the UK and through its various phases the vast majority of UK anaesthetists. This project has also involved considerable multidisciplinary working with both allergists and immunologists. The project could not take place without the generous voluntary efforts of many

people and we acknowledge that here and offer them our thanks. The projects require anaesthetists to report cases where a significant critical incident has occurred, and harm may have come to the patient. We rely on anaesthetist's openness and honesty. The NAP6 panel, including the Clinical Lead, had no access to any information regarding the geographical source of the report, the identity of the reporter, or any patient, hospital or clinician identifiable details. This anonymity, provided within the project design remains central to its success.

Declaration of interest

TMC: is an associate editor of the British Journal of Anaesthesia. He is not aware of any financial conflicts.

NH, LF, TG, KFl, SM, HT, AW, NMcG, KFe, JH, WE, HK, MT, DNL, SN, SK, K-LK, SF, MB and AMcG all declare they have no conflicts of interest.

SRM is the Director of the NIAA Health Services Research Centre which commissioned this study.

Funding

Funded by the Royal College of Anaesthetists.

Acknowledgements

We thank all anaesthetists who engaged with the NAP6 project and all local coordinators who administered the project at each of the participating hospitals. Particular thanks to Dr Martin Shields, Consultant Anaesthetist, Belfast Health and Social Care Trust, who acted as NAP6 Moderator throughout the project. At the Royal college of Anaesthetists, we thank Mr James Goodwin, Research Manager, Mr Jose Lourtie, Research Supervisor, Ms Sharon Drake, Director of Education and Research. We also acknowledge the contributions of the following NAP6 panel review members Dr Guy Scadding, Consultant Allergist, Royal Brompton and Harefield NHS Foundation Trust, London; Dr Thirumala Krishna, Consultant Immunologist, Heart of England NHS Foundation Trust, Birmingham; Ms Ruth Collins, Staff Nurse, Hillsborough Private Clinic (The Association for Perioperative Practice); Ms Mandy East, Former National Coordinator of the Anaphylaxis Campaign (Anaphylaxis Campaign).

Authors' contributions and authorship

TMC – Co-designed methodology of the study. Analysed results. Wrote all drafts of the paper and the final draft.

NH – Co-designed the methodology of the study. Analysed results. Reviewed and revised early drafts of the paper and the final draft.

LF - Contributed to design and methodology of the study. Administered study. Took part in review of draft manuscript leading to finalisation.

All other panel members contributed to the design and methodology of the study, reviewed the results and took part in review of draft manuscripts leading to finalisation.

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Table 1. Grading of perioperative hypersensitivity/anaphylaxis used for determining inclusion or exclusion in the NAP6 project.

Grade	Features	NAP6
1 *Not life-threatening*	Rash, erythema and/ or swelling	Hypersensitivity - Excluded
2 *Not life-threatening*	Unexpected hypotension – not severe e.g. not requiring treatment and/or bronchospasm – not severe e.g. not requiring treatment +/- Grade 1 features	Hypersensitivity - Excluded
3 *Life-threatening*	Unexpected severe hypotension and/or severe bronchospasm and/ or swelling with actual or potential airway compromise +/- Grade 1 features	Included if perioperative anaphylaxis suspected.
4 *Life-threatening*	Fulfilling indications for CPR	Included if perioperative anaphylaxis suspected.
5 Fatal	Fatal	Included if perioperative anaphylaxis suspected.

Table 2. Degree of physical harm. Source: NPSA Seven steps to patient safety[23]

Severity grade	Description (tick against the most severe feature)
Uncertain	Insufficient information
Mild	Minimal harm necessitating extra observation or minor treatment*
Moderate	Significant, but not permanent harm, or moderate increase in treatment** Includes delayed cancer surgery (Q 27.9)
Severe	Permanent harm due to the incident***, Also including cardiac arrest (Q 14.1); adverse sequelae recorded as "Severe" in Part A (page 26) or Part B (page 4,5); ICU stay of 14 days or longer (Q 23.8)
Death	Death due to the incident

* first aid, additional therapy or additional medication. Excludes extra stay in hospital, return to surgery or readmission.

** return to surgery, unplanned re-admission, prolonged episode of care as in or out patient or transfer to another area such as intensive care.

*** permanent lessening of bodily functions, sensory, motor, physiologic or intellectual.

Table 3 Immunological classification of events in NAP6

Class of event *In addition to history of reaction grade 3,4,5*	High certainty	Intermediate certainty
Allergic anaphylaxis (IgE-mediated)	Timeline – within 60 min Evidence of mast cell mediator release -tryptase Evidence of positive sIgE (blood or skin tests)* Differential diagnoses excluded 4/4 criteria; *essential	Timeline - within 60 min Evidence of mast cell mediator release -tryptase Evidence of positive sIgE (blood or skin tests)* Differential diagnoses excluded 3/4 criteria; *essential
Non-allergic anaphylaxis (non IgE-mediated)	Timeline – within 60 min Evidence of mast cell mediator release -tryptase *(see note 2)* *No evidence of* positive sIgE (blood or skin tests) Differential diagnoses excluded 4/4 criteria	Timeline – within 60 min Evidence of mast cell mediator release -tryptase *No evidence of* positive sIgE (blood or skin tests) Differential diagnoses excluded 3/4 criteria
Anaphylaxis – mechanism uncertain	Timeline – within 60 min Evidence of mast cell mediator release -tryptase Skin tests or blood sIgE not available 3/3 criteria	
Anaphylaxis uncertain	Meeting 2/3 criteria in 3 above and/or Differential diagnoses more likely: Airway management Drug side effect Drug overdose Cardiac disease/event	
Not anaphylaxis	Not meeting clinical criteria for diagnosis (as per grading)	

Table 4. The 199 identified culprit agents in 193 cases of anaphylaxis in NAP6.

Drugs by class			
	Definite	Probable	Total
Antibiotics	67	27	94
NMBA	49	16	65
Chlorhexidine	14	4	18
Patent blue	8	1	9
Others	10	3	13
All	148	51	199
Antibiotics			
Co-amoxiclav	38	8	46
Teicoplanin	21	15	36
Cefuroxime	2	2	4
Gentamicin	1	2	3
Flucloxacillin	2	0	2
Tazocin	1	0	1
Vancomycin	1	0	1
Metronidizole	1	0	1
NMBAs			
Rocuronium	21	6	27
Atracurium	14	9	23
Suxamethonium	13	1	14
Mivacurium	1	0	1
Antiseptics and Dyes			
Chlorhexidine	14	4	18
Patent blue	8	1	9
Other agents			
Gelatin	3	0	3
Blood products	2	0	2
Ondansetron	1	1	2
Sugammadex	1	0	1
Ibuprofen	1	0	1
Propofol	1	0	1
Protamine	1	0	1
Aprotinin	0	1	1
Enoxaparin	0	1	1

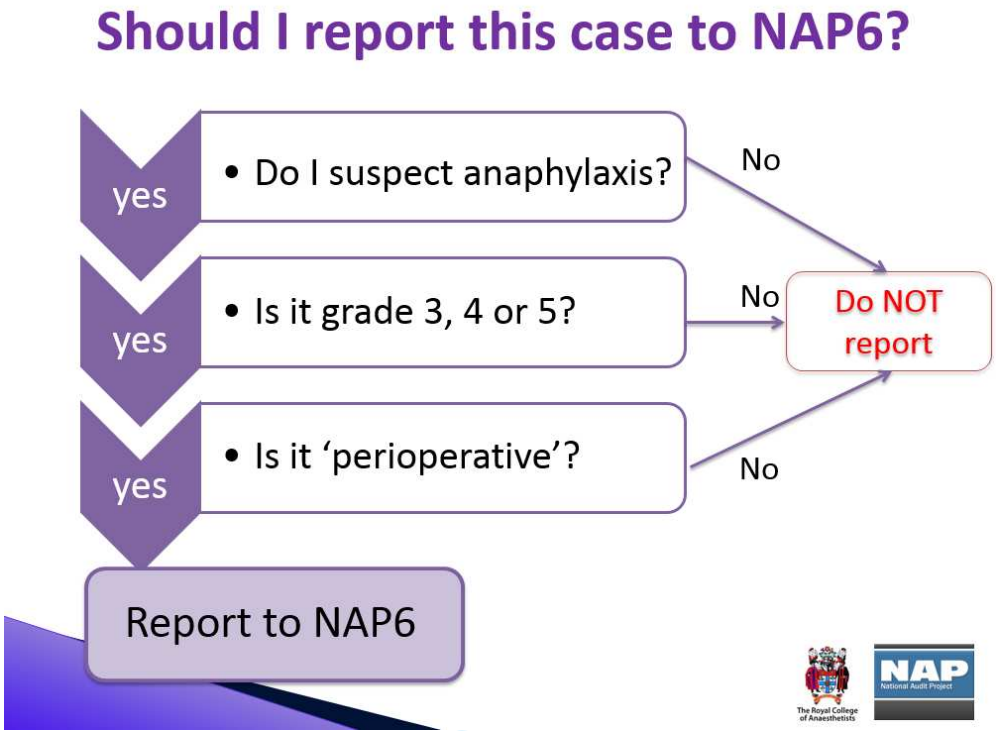

Figure 1. Supporting information on which cases should be reported to NAP6.

Appendix 1. Panel review form.

DATE OF REVIEW: CASE ID:

Does the report meet the inclusion criteria? ☐ Yes ☐ No
If no, why:

Might it be a duplicate? ☐ Yes ☐ No
If yes, action taken:

Is the report interpretable? ☐ Yes ☐ No
If no, action taken:

Timing of event ("induction" refers to first drug/substance administered by the anaesthetist)
☐ Pre-induction ☐ After induction and before surgery/intervention
☐ During surgery/intervention ☐ After completion of surgery/intervention

Class of event (as determined by review panel)
☐ Allergic anaphylaxis ☐ Non-Allergic anaphylaxis ☐ Anaphylaxis, mechanism uncertain
☐ Not anaphylaxis ☐ Uncertain ☐ Not stated

Class of event (as determined by allergy clinic)
☐ Allergic anaphylaxis ☐ Non-Allergic anaphylaxis ☐ Anaphylaxis, mechanism uncertain
☐ Not anaphylaxis ☐ Uncertain ☐ Not stated

Grade of event as determined by review panel: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Uncertain

Immediate care (tick)

	Yes	No	Unclear	N/A
Resuscitation by anaesthetist of appropriate grade				
Prompt recognition of critical event				
Prompt recognition of anaphylaxis				
Appropriate airway management				
Prompt pharmacological treatment for anaphylaxis				
Comprehensive pharmacological treatment for anaphylaxis				
Prompt initiation of cardiac compressions				
Administration of adrenaline when indicated				
Appropriate iv fluid management				
Suspected culprit agent discontinued promptly				
Actual culprit agent discontinued promptly				

Intervention abandoned appropriately				

Clinical management by the anaesthetist:

☐ Good ☐ Poor ☐ Good and poor elements ☐ Un-assessable

Subsequent care (tick)

	Yes	No	Unclear	N/A
Transfer to different hospital for HDU/ICU				
Written information given to patient prior to clinic appointment				
Appropriate MCT samples requested				
Appropriate MCT results available				
Investigation impacted by un-actioned MCT sample request(s)?				
Was the patient referred to an allergy clinic if appropriate?				
Was adequate information provided to the allergy clinic at referral?				
Was the clinic waiting time significantly detrimental to the patient?				
Patient given written information by anaesthetist prior to clinic appointment				
Patient given hazard warning e.g., Medic Alert by anaesthetist				
Case reported to MHRA by anaesthetist				

Referral to allergy clinic:

☐ Good ☐ Poor ☐ Good and poor elements ☐ Un-assessable

Allergy clinic investigation (tick)

	Yes	No	Unclear	N/A	if no specify
All potential culprits investigated					
Sufficient panel of muscle relaxants*					
Chlorhexidine investigated*					
Latex investigated*					
Appropriate SPTs*					
Appropriate IDTs*					
Appropriate blood tests					
Was it necessary to measure baseline MCT in clinic					
Appropriate challenge tests					
Appropriate advice on future avoidance					
Written information to patient e.g. copy of clinic letter					
Clinic letter to anaesthetist					
Clinic letter to GP					
Patient given Hazard Warning e.g. Medic Alert by clinic					
Case reported to MHRA by clinic					

* see crib sheet

Allergy clinic investigation:

☐ Good ☐ Poor ☐ Good and poor elements ☐ Un-assessable

Culprit agent(s)

Identity of drugs/substance suspected by:	Drug/substance 1	Certainty H/I/L/Not stated	Drug/substance 2	Certainty H/I/L/Not stated	Unable to identify (tick)	Not recorded (tick)
Anaesthetist						
Allergy clinic						
Review panel						

CONTRIBUTORY AND CASUAL FACTORS

Specific (tick those that apply)

	Yes	No	Unclear	N/A
Incomplete pre-intervention allergy history				
Pre-intervention allergy history not heeded				
Possibility of cross-sensitivity not heeded				
A previous reaction was not appropriately investigated				

Was the index event preventable? ☐ Yes ☐ No ☐ Uncertain

If yes, how might it have been prevented?

If there was a further reaction, could it have been prevented?

☐ Yes ☐ No ☐ Uncertain ☐ N/A

If yes, how might it have been prevented?

SEVERITY OF PHYSICAL HARM (NPSA)

This is the harm occasioned by the whole episode (see crib sheet)

Severity grade	Description (tick against the most severe feature)	Tick
Uncertain	Insufficient information	
None	No harm (whether lack of harm was due to prevention or not)	
Low	Minimal harm necessitating extra observation or minor treatment	
Moderate	Significant, but not permanent harm, or moderate increase in treatment	
Severe	Permanent harm due to the incident	
Death	Death due to incident	

DEPARTURE FROM GUIDELINES

Significant departure from:	Unclear	N/A	Yes	No	If yes specify
AAGBI Safety Guidelines					
RCUK Guideline					
BSACI Guideline on investigation					

Lessons to be learned:

Any possible recommendations arising:

Amend Summary Narrative (i.e. modify draft prepared by NH) ☐ Yes ☐ No

Action taken:

Consider: Any further information needed. If yes, action taken:

Is this case suitable for a vignette? ☐ Yes ☐ No. If yes, why?